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PREVENTION OF VENOUS THROMBOSIS AND PULMONARY EMBOLISM

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Introduction and Overview

Venous thrombosis and pulmonary embolism constitute major health problems that result in significant morbidity and mortality in the United States. It is estimated that venous thrombosis and pulmonary embolism are associated with 300,000 to 600,000 hospitalizations a year and that as many as 50,000 individuals die each year as a result of pulmonary embolism.

Both venous thrombosis and pulmonary embolism are often silent and difficult to detect by clinical examination. The use of a number of diagnostic tests such as fibrinogen uptake, Doppler ultrasound, impedance plethysmography, venography, ventilation-perfusion scans, and pulmonary angiography has resulted in the identification of several groups of patients at high risk of developing venous thromboembolic disease. Patients undergoing various types of surgery—general, orthopedic, gynecological-obstetrical, urological, and neurosurgical—are at high risk for developing deep venous thrombosis (DVT) and pulmonary embolism (PE). Of these groups, orthopedic patients appear to be especially prone to thrombosis, particularly patients with hip fracture. Patients with various types of medical diseases, usually chronic, are also at high risk for venous thrombotic events.

Because some groups of patients at high risk for the development of venous thromboembolism can be identified, it is reasonable and desirable to consider ways of prevention; prevention is far superior to treatment.

To help resolve questions that relate to various rophylactic measures in high-risk groups of patients, the National Heart, Lung, and Blood Institute and the NIH Office of Medical Applications of Research convened a Consensus Development Conference on Prevention of Venous Thrombosis and Pulmonary Embolism on March 24-26, 1986. After hearing a series of expert presentations and discussion from the audience and reviewing the medical literature, a consensus development panel representing the professional fields of vascular, orthopedic, urologic, and trauma surgery, hematology, pulmonary medicine, obstetrics and gynecology, family practice, epidemiology, biostatistics, and the general public considered the evidence and agreed on answers to the following questions:

- What is the level of risk of venous thrombosis and embolism in various patient groups?
- What is the efficacy and safety of various forms of prophylaxis in these patient groups?
- What are the recommended forms of prophylaxis in these patient groups?
- What questions remain to be answered about prophylaxis of venous thromboembolism?

Inherent in the first three questions is an epidemiologic and statistical assessment of whether the existing data are sufficient to warrant recommendations on the prophylaxis of venous thromboembolism.

The most rigorous and definitive test of any method of prophylaxis is the randomized clinical trial. However, the incidence of clinically significant PE is low and would thus require trials on the order of 5,000 patients to examine the effect of prophylaxis on all PE or 100,000 patients to examine the effect on all-cause mortality. In contrast, the incidence of DVT is substantially higher, ranging from 20 to 70 percent. Thus, prophylactic treatment of DVT can be evaluated with trials of smaller sample size, but it is first necessary to demonstrate the clinical relevance of the presence of DVT to the development of pulmonary embolism.

The use of DVT screening tests as a marker for pulmonary embolism is justified both by the known pathophysiology of pulmonary embolism

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and the association of a reduction in DVT with a reduction in PE. In particular, the combined data on over 12,000 individuals in randomized clinical trials of low-dose heparin showed a 68 percent reduction in DVT as measured by the ^{125}I-fibrinogen uptake test and/or venography; this was associated with a 49 percent reduction in PE. Moreover, there was a decrease in overall mortality that was due to the decrease in fatal pulmonary embolism. The evidence for a benefit of prophylaxis in preventing pulmonary embolism is compelling using DVT as a marker. The findings within most specific patient subgroups rely on this assumption: that DVT is an appropriate marker for PE.

When using DVT as a marker for PE, many clinical trials have had an inadequate number of patients to detect important therapeutic differences. Trends that may appear to be a chance finding in any one trial assume importance when consistently seen in multiple trials. In evaluating the evidence, the panel has assessed each trial as it stands alone and has searched for consistency among trials with similar therapy and patient groups.

The panel has also evaluated the evidence from all clinical trials presented at the conference and addressed each question as it relates to specific patient groups at high risk for the development of venous thromboembolic events.

1.

What is the level of risk of venous thrombosis and embolism in various patient groups?

Venous thrombosis and PE constitute major causes of morbidity associated with many common medical conditions and surgical procedures. Reliable natural history data are available from the control arms of well over 100 clinical trials published during the past two decades, generally from patients over the age of 40. European trials document a higher rate of DVT than has been reported in North America, Asia, or Africa, but a significant incidence of these complications has been found in all studies directed at this problem, regardless of the location of the investigation.

General Surgery

The largest pool of data has been obtained in studies of patients over the age of 40 undergoing general surgical procedures, where the average incidence of deep venous thrombosis in control patients is 25 percent by fibrinogen scanning and 19 percent by venography. The pooled data incidence of DVT in Europe is 30 percent, and in North America it is 16 percent. DVT extends proximal to the knee joint in 7 percent, and clinically significant pulmonary embolism occurs in 1.6 percent of the general surgical population. Finally, the likelihood of a major pulmonary embolus leading to death approaches 1 percent. Advancing age and malignancy are associated with even higher rates of both DVT and PE.

Orthopedic Surgery

All elective orthopedic surgical patients undergoing lower extremity surgery are at risk for deep venous thrombosis. The risk to patients is greatest for hip surgery and knee reconstruction, where DVT rates range from 45 to 70 percent.

Clinically significant PE has been reported to be as high as 20 percent in hip surgery patients, with a 1 to 3 percent incidence of fatal PE. The rates of both clinical PE and fatal PE following knee reconstruction are lower than following hip surgery but remain a problem.

Urology

The incidence of DVT in urologic surgery is similar to that in general surgery, that is, about 25 percent, and ranges from 40 percent in transvesical prostatectomy to 10 percent in transurethral surgery. Because increasing age has a high correlation with increased risk of DVT, urologic patients often have a higher risk than other surgical patients.

Gynecology and Obstetrics

The reported overall risk of DVT in gynecologic surgery ranges from 7 to 45 percent. Fatal PE is estimated to occur in nearly 1 percent of these patients. Low-risk patients include those up to 40 years of age undergoing surgical procedures of less than 30 minutes, and in this group, the incidence of DVT is under 3 percent. Moderate-risk patients, 40 to 70 years of age, undergoing minor or major surgery with no other risk factors, have a 10 to 40 percent risk of DVT. High-risk patients, age 40 or over with added risk factors (prior DVT/PE, varicose veins, infection, malignancy, estrogen therapy, obesity, and prolonged surgery), have a 40 to 70 percent risk of DVT and a 1 to 5 percent risk of fatal PE.

The risk of DVT in pregnancy has been reported to be five times higher than in nonpregnant patients in the same age group and may be increased post partum. Antenatal risks are increased in patients with prior DVT or PE, varicose veins, and obesity. It is not known whether these risks are additive. Postpartum risks are increased by Cesarean delivery, which carries risks similar to those of gynecologic surgery.

Neurosurgery and Neurology

The risk of DVT and fatal PE in neurosurgical patients is similar to

that of other surgical high-risk groups. The incidence of DVT ranges from 9 to 50 percent. Fatal PE occurs in from 1.5 to 3 percent. In stroke, the risk of DVT in the paralyzed leg is as high as 75 percent, whereas in the nonparalyzed leg it is approximately 7 percent.

Trauma

The risks of thromboembolic diseases and subsequent PE have not been specifically defined for the general trauma population. This is due in part to the complex nature and wide variety of systems injured. In addition, the most prevalent diagnostic test used for DVT, the ^{125}I-fibrinogen uptake, cannot be used effectively in this population because tissue trauma itself can produce a positive scan. Although data are lacking, it is estimated that the incidence of DVT in the young multisystem trauma patient is about 20 percent. The incidence of fatal PE is not known. Two subgroups of trauma patients have a much higher risk of thrombosis. The elderly patient with a hip fracture has a reported incidence of DVT exceeding 40 percent and an incidence of fatal PE exceeding 4 percent. The patient with an acute head or spinal cord injury has a reported 40 percent incidence of DVT and a greater than 1 percent incidence of fatal PE.

Medical Conditions

Two groups of medical conditions exist in which the incidence of thromboembolism is greatly increased (table 1). One group consists of inherited deficiencies of inhibitors and regulators of coagulation or fibrinolysis. These inherited conditions are associated with a positive family history for thromboembolism, onset at an early age, and repeated episodes of thromboembolism, often in the absence of other known predisposing factors. Although the exact cumulative risk of thromboembolism is not known in most of these uncommon genetic disorders, it approaches 80 percent in antithrombin III deficiency.

A much larger group encompasses patients with acquired conditions predisposing to thromboembolism. The risk of thromboembolism in this group of patients ranges up to 80 percent in paroxysmal nocturnal hemoglobinuria, up to 70 percent in congestive heart failure, and up to 40 percent in acute myocardial infarction.

In patients from either category, the risk for thromboembolism is heightened by the presence of additional risk factors—but by an unknown amount.

Table 1
Risk Factors Predisposing to Thromboembolism

1. Inherited Risk Factors
   - A. Antithrombin III deficiency
   - B. Protein C deficiency
   - C. Protein S deficiency
   - D. Dysfibrinogenemia
   - E. Disorders of plasminogen and plasminogen activation

2. Acquired Risk Factors
   - A. Lupus anticoagulant
   - B. Nephrotic syndrome
   - C. Paroxysmal nocturnal hemoglobinuria
   - D. Cancer
   - E. Stasis—congestive heart failure, myocardial infarction, cardiomyopathy, constrictive pericarditis, anasarca
   - F. Advancing age
   - G. Estrogen therapy
   - H. Sepsis
   - I. Immobilization
   - J. Stroke
   - K. Polycythemia rubra vera
   - L. Inflammatory bowel disease
   - M. Obesity
   - N. Prior thromboembolism

2.

What are the efficacy and safety of various forms of prophylaxis in these patient groups?

Several prophylactic therapies for DVT and PE have been adequately evaluated. In appropriate prospective randomized clinical trials, clear and statistically significant benefit has been demonstrated. Both pharmacologic and physical modalities have been tested, singly and in various combinations. The best documentation of benefit in decreasing DVT, PE, fatal pulmonary embolism, and overall mortality has been associated with trials of low-dose heparin. Other effective prophylactic modalities include dextran, external pneumatic compression, and graduated compression elastic stockings.

General Surgery

Within the broad scope of general surgery, low-dose heparin administered subcutaneously every 8 or every 12 hours beginning 2 hours prior to surgery reduces the rate of DVT by 60 percent, for a net decrease in incidence from 25 percent to 10 percent. In pooled studies, the likelihood of a calf thrombus extending proximally is reduced by approximately one-half, as is the risk of clinically significant PE. Finally, fatal PE decreases from 0.7 to 0.2 percent. Heparin-associated thrombocytopenia has been reported rarely in patients receiving low-dose heparin.

Although fewer data are available, dextran-70 exerts a comparable protective effect in decreasing PE, but a lesser decrease in DVT. Dextran-40 appears to have a similar effect. The use of a combination of dihydroergotamine and heparin, as well as the use of external pneumatic compression, produce comparable benefits with respect to DVT, but fewer patients have been studied with these modalities. The use of

graduated compression elastic stockings has also been reported to be of benefit, but even fewer patients have been studied and stockings must be carefully fitted if they are to have prophylactic merit. The likelihood of benefit with any of these methods suggests that the prophylactic treatment of 200 patients will prevent 1 death from PE, 1.2 episodes of clinically significant PE, and 20 episodes of DVT. No benefits were associated with aspirin prophylaxis. Both heparin and dextran increase the risk of bleeding and hematoma formation, but the risk of serious complications or death is minimal. The side effects of external pneumatic compression and elastic stockings are limited to patient discomfort and subsequent failure of compliance.

Orthopedic Surgery

Despite the effectiveness of low-dose heparin in other situations, it may be less beneficial in orthopedic patients. Dextran and warfarin have been shown to reduce the incidence of DVT by a factor of two in controlled trials in patients undergoing elective hip surgery and knee reconstruction. Rates of clinical PE are also reduced, but the lowered death rate from PE, while suggestive, is not statistically significant.

Elevation of the foot of the bed, gradient elastic stockings, and external pneumatic compression also reduce the incidence of DVT significantly. The use of these mechanical measures is without known complications.

Warfarin and dextran in commonly used doses can cause complications of operative bleeding and wound hematomas. Congestive heart failure, renal failure, and anaphylaxis are uncommon complications of dextran. Fatal hemorrhage has been reported with warfarin. The incidence of these bleeding complications is not well documented in orthopedic surgery. Wound hematomas can be a significant problem in joint replacement patients. Small-scale studies suggest that low-dose warfarin may be safe, but the data are limited.

Urology

The efficacy of prophylaxis for DVT in urologic patients has been studied most extensively with low-dose heparin. In several studies, the reduction in incidence following prophylaxis is 75 percent—similar to data from general surgery. Small-scale studies using external pneumatic compression suggest a decrease in DVT similar to that in patients receiving low-dose heparin.

Low-dose heparin appears safe as measured by transfusion requirements and the postoperative decrease in hemoglobin concentration. External pneumatic compression also appears to carry no significant risk.

Gynecology and Obstetrics

The evidence suggests that for low-risk patients with little chance of DVT, early ambulation and graduated compression stockings are sufficient prophylaxis. Patients at moderate to high risk, with benign disease, can be managed effectively with low-dose heparin, dextran, and/or external pneumatic compression with comparable results. Some evidence suggests that low-dose heparin is ineffective for prophylaxis in patients with gynecologic malignancy. In this category, dextran, warfarin, and/or external pneumatic compression can be effective. Although data are lacking, the panel believes that warfarin also may provide effective and safe prophylaxis for patients with benign or malignant disease.

Data from controlled trials are lacking for pregnant and postpartum patients. However, the panel believes that low-dose heparin may be effective and safe for prophylaxis when used antenatally in pregnant patients at risk. There are no data regarding the optimal timing of therapy. Warfarin prophylaxis is contraindicated in pregnancy, and there are no data on the use of dextran in pregnancy. The panel believes that low-dose heparin and/or external pneumatic compression may be effective and safe in prophylaxis in postpartum patients at risk.

Neurosurgery and Neurology

There is a relative paucity of studies on specific therapies for special subgroups of neurosurgical patients as compared with general and orthopedic surgery patients. The efficacy of external calf compression, low-dose heparin (with or without dihydroergotamine), and warfarin has been demonstrated for patients with extracranial problems.

Patients with intracranial lesions and spinal lesions for which even minor bleeding complications could have disastrous effects are generally not considered candidates for prophylaxis with anticoagulants, although limited data support the use of low-dose heparin as safe for selected craniotomy patients. External pneumatic compression is recommended for patients with this group of problems and has been shown to be both efficacious and safe.

Trauma

Because hemorrhage is a major complication of traumatic injury, trauma-induced bleeding must be controlled prior to the use of any agent that might accentuate the bleeding process. The efficacy and safety of the various forms of prophylaxis have not been evaluated in the multisystem trauma patient population, but a number of specific patient subgroups have been

studied. In young patients with musculoskeletal trauma, low-dose heparin (with or without dihydroergotamine) and dextrans have been studied. When begun within the first 2 days, these agents decrease the rate of DVT. Increased bleeding is seen with these methods, but the incidence is no greater than that encountered with their use in elective orthopedic surgery Patients. A number of prophylactic measures have been studied in high-risk hip fracture patients. Aspirin and low-dose heparin have not been shown to be effective. Dextran has been shown to decrease the incidence of DVT. Although bleeding complications are increased, the use of dextran-40 in doses not exceeding 10 ml/kg in the first 24 hours and 5-7 ml/kg every 24 hours after this point decreases this problem. Warfarin in elderly patients with hip fractures decreases the incidence of both DVT and pulmonary emboli. Bleeding complications are increased, but the problem can be minimized if the increase in prothrombin time does not exceed 1.4 times control. External pneumatic compression has also been shown to decrease the incidence of DVT. There are some data to indicate that pressure gradient stockings are also effective.

Anticoagulants have not been used in the acute head injury patient because of the risk of bleeding. External pneumatic compression has been shown to decrease the incidence of DVT in this group. Both low-dose heparin and external pneumatic compression are effective in reducing DVT in trauma-induced paraplegia.

Medical Conditions

Several approaches are available to decrease the risk of thromboembolism in patient groups listed in table 1. These treatments include low-dose heparin, warfarin, and early ambulation and other physical methods. One study reported that administration of low-dose heparin decreased all-cause mortality from 10 percent to 5 percent for patients with a wide variety of medical conditions. Low-dose heparin reportedly decreases the incidence of DVT in persons hospitalized for acute myocardial infarction, heart failure, and/or pulmonary infection. Data are lacking for other prophylactic methods. Because of the synergistic nature of an underlying thrombotic tendency and the added risk of an acute condition or a surgical procedure in some medical patients, low doses of heparin may be inadequate for prophylaxis. The risk of hemorrhage from prophylactic methods is no higher in medical than in general surgical patients receiving these treatments and, in fact, is lower in the absence of a surgical wound.

3.

What are the recommended forms of prophylaxis in these patient groups?

General Surgery

Available data justify routine prophylaxis of all surgical patients in high-risk situations. In high-risk patients—those over the age of 40, or obese, or with malignancy, or prior DVT or PE, or undergoing large or complicated surgical procedures—prophylactic treatment with low-dose heparin using 5,000 U subcutaneously every 8 or 12 hours is recommended, at least until the patient is ambulatory. Dextran in initial doses of 10 ml per kg appears equally effective in decreasing PE but is more expensive. Most studies have employed dextran-70 but the fewer studies with dextran-40 suggest it is equally effective.

Both external pneumatic compression and gradient elastic stockings are also effective modalities in preventing DVT. The addition of dihydroergotamine to the same dose of heparin may be more efficacious, but the contraindications and potential risks associated with its vasoconstrictive effects must be borne in mind by physicians selecting this modality. The need for prophylaxis in patients under 40 with no known risk factors undergoing uncomplicated operative procedures lasting less than 1 hour is unknown.

Orthopedic Surgery

For high-risk orthopedic patients undergoing elective hip surgery or knee reconstruction, one of the following prophylactic regimens is recommended for at least 7 days or longer if the patient remains bedridden: low-dose warfarin, dextran, or adjusted-dose heparin. For other patients, mechanical measures, including gradient elastic stockings or external pneumatic compression, may be used if feasible. Early mobilization and elevation of the foot of the bed or of injured limbs are also recommended.

Urology

Because the low-dose heparin prophylaxis data document both efficacy and safety, this therapy should be used in urologic patients over the age of 40. The use of mechanical modalities such as external pneumatic compression offers a possible attractive alternative, although more trials are necessary in urologic patients.

Gynecology and Obstetrics

Evidence indicates that low-risk gynecologic patients are satisfactorily managed with early ambulation and graduated compression stockings. Patients at moderate and high risk (exclusive of those with gynecologic malignancy) should be managed with low-dose heparin and/or external pneumatic compression. Dextran is an alternate choice. Patients with gynecologic malig-

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nancy should be managed with dextran and/or external pneumatic compression until fully ambulatory. Some evidence suggests that patients with gynecologic malignancy can be managed with low-dose heparin combined with external pneumatic compression. The panel believes that warfarin may be a useful alternative in patients with benign or malignant disease.

A reduction of risk factors, such as the discontinuance of contraceptive pills or estrogen therapy prior to surgery, is recommended in all elective surgical patients.

Although data regarding prophylaxis of DVT in pregnancy and the postpartum period are limited, the panel believes that patients with a prior history of DVT/PE may be treated antenatally with low-dose heparin. The time of onset of therapy is arbitrary, as no clear recommendation is supported by the literature. Pregnant patients with other risk factors should have their prophylactic management individualized. The panel believes that postpartum patients at risk should be managed with low-dose heparin and/or external pneumatic compression according to the level of risk until fully ambulatory.

Neurosurgery and Neurology

Prophylactic regimens must be considered by specific subgroup of neurosurgical conditions. For patients undergoing craniotomy for tumor, subarachnoid hemorrhage, AV malformation, aneurysm, arterial bypass, shunting procedures, and other intracranial problems, external pneumatic compression is recommended. This modality is effective in reducing the risk of DVT and avoids those potential hemorrhagic complications of antithrombotic therapies that, even if minor, may be disastrous in neurosurgical cases.

For extracranial neurosurgical problems such as elective spinal cord surgery and laminectomy, external pneumatic compression and low-dose heparin are equally effective and are recommended, either alone or in combination.

Stroke patients in whom hemorrhagic stroke has been excluded by CT scan should receive low-dose heparin. For all other stroke patients, external pneumatic compression is recommended. Neurosurgical and stroke patients who remain bedridden for more than 5 days should receive prophylaxis until ambulatory. No studies provide information regarding the use of gradient compression stockings, physical therapy, or early ambulation as modes of prophylaxis either singly or in conjunction with other recommended modalities.

Trauma

The specific risks of bleeding dictate the manner and type of prophylaxis to be used in the trauma patient. The elderly patient with a hip fracture is at high risk for thromboembolic complications and clearly requires some form of prophylaxis for at least 7 days or until ambulatory. One can choose from three effective measures: dextran, external pneumatic compression, or pressure gradient elastic stockings may be useful. The efficacy of low-dose warfarin in hip fracture patients is not known. Aspirin and low-dose heparin are of no benefit.

Head injury and acute spinal cord injury patients also require prophylaxis. To minimize the high risk of bleeding, external pneumatic compression and pressure gradient elastic stockings are the methods of choice.

For severe musculoskeletal trauma, prophylaxis is indicated until the patient is ambulatory. Low-dose heparin or dextran is effective in young patients if initiated early. External pneumatic compression and gradient compression stockings are effective alternatives for decreasing lower leg thrombosis if lower extremity trauma does not preclude their use. In multisystem trauma, anticoagulants should be used with caution until the types of injuries present have been assessed and initial bleeding controlled.

Medical Conditions

Limited clinical trials support the use of low-dose heparin for patients with heart failure, acute myocardial infarction, or pulmonary infection to prevent DVT. Although studies do not exist to support extension of these observations to other medical patients at bed rest and at risk for thromboembolism, administration of low-dose heparin may be indicated, especially as long as other conditions predisposing to DVT coexist. Where long-term prophylaxis is indicated in chronic high-risk patients, warfarin therapy is appropriate.

4.

What questions remain to be answered about prophylaxis of venous thromboembolism?

Many issues regarding the prophylaxis of venous thromboembolism remain unresolved. Answers to these questions will require randomized clinical trials as well as basic research on mechanisms. The fundamental issues that need to be examined include:

1. The determination of the basic mechanisms associated with thrombus formation and dissolution and development of specific assays that reflect thrombus formation and dissolution so that the patients who truly need prophylactic therapy can be identified and special risk circumstances can be avoided.

2. The elucidation of the natural history of an acute thromboembolic event and determination of the long-term sequelae and the effects of prophylaxis. In particular, the relationship of the postphlebitic syndrome with DVT needs to be explored.
3. The explanation of observed geographic and racial differences in the frequency of venous thromboembolic disease so that potential therapeutic applications can be targeted for high-risk patients.
4. The development of better techniques for the diagnosis of DVT and PE.
5. The development of prophylactic therapies that restore normal intravascular homeostasis so that both thrombosis and bleeding complications are minimized.
6. The determination of the optimal intensity of antithrombotic therapy to treat effectively and safely the diverse patient problems encountered.
7. The further evaluation of the role of various prophylactic therapies for DVT and PE in medical conditions, pregnancy and trauma by prospective randomized clinical trials.
8. The determination of efficacious and safe prophylactic therapy for venous thromboembolism in patients undergoing the commonly performed procedure of coronary artery bypass surgery and coronary angioplasty.
9. The worldwide standardization of laboratory tests to monitor anticoagulation therapy to facilitate comparisons between various patient populations and geographic locations.

Conclusions

The major conclusions of the consensus panel are that:

- Deep venous thrombosis and pulmonary embolism constitute major health problems in the United States.
- Groups of high-risk patients have been identified.
- Deep venous thrombosis and pulmonary embolism in these patients can be significantly reduced by prophylactic regimens, which should be used more extensively.
- Regimens recommended for prevention of deep venous thrombosis and Pulmonary embolism include low-dose heparin, adjusted-dose heparin, dextran, and warfarin. Low-dose warfarin, external pneumatic compression, and gradient elastic stockings alone or in combination with heparin or heparindihydroergotamine are also effective in decreasing DVT which the panel considers to be an indicator of their effects on pulmonary embolism. Aspirin has not been shown to be beneficial.
- None of these preventive measures is ideal, but most are relatively simple to use; complications are generally minor; and the need for laboratory monitoring is minimal.
- Effective prophylactic regimens differ, according to the type of patient at high risk. Prophylactic therapy should be tailored according to the patient's disease and degree of risk.
- In some groups of patients, more than one effective prophylactic regimen is available.

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